Analysis and Comment regarding EPA description of Human Incident Data found in the "Impact Assessment for Proposed Rodenticide Mitigation (DP 332577)"

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TABLE OF CONTENTS

	Page
Executive Summary	3
Background	4
Specific comments regarding EPA human incident analysis	5
New Published Data not included in the EPA proposed Risk Mitigation Procedures	9
Key findings and considerations weighing in on the consensus panel conclusions	9
Background Information regarding the Genesis of the LAAR Consensus Panel Initiative	10
Composition of the Review Committee	10
Data Reviewed	11
Conclusions Reached Regarding Children (age <6 years old or less)	11
About the Author	12

Executive Summary:

Human incident data involving accidental pediatric exposures to long acting anticoagulant rodenticides (LAAR) has been presented by EPA in support of proposed mitigation procedures. The single largest category of human incidents and the category of incidents that is targeted by the proposed mitigations is acute, accidental pediatric exposures to LAAR's. A primary focus of the proposed mitigations relates to preventing these accidental pediatric exposures which is expected to result in "health benefits associated with reduced illnesses and deaths." EPA has also suggested that there are unacceptable "social costs associated with treating children who might have been exposed and emotional toll of suspected exposure incidents."

The EPA pediatric exposure analysis is based on three years of aggregated data derived from annual reports of the Toxic Exposure Surveillance System (TESS) which is compiled and published by the American Association of Poison Control Centers (AAPCC). There are serious flaws in both the interpretation and presentation of this data by EPA as it relates to the clinical risk of injury from accidental pediatric exposures to LAAR's.

First, there are no pediatric "deaths" to prevent. Nor are there any documented pediatric injuries attributed to LAAR toxicity that have resulted from acute, unintentional exposures to the LAAR's. A detailed analysis of the data that EPA reviewed is provided in this document to support this fact. Additionally, a landmark scientific article regarding a comprehensive review of pediatric exposures to long acting anticoagulation rodenticides (LAAR's) has been published subsequent to the publishing of the EPA proposed mitigations. This national consensus paper entitled "Long-acting anticoagulant rodenticide poisoning: An evidence-based consensus guideline for out-of-hospital management" unequivocally confirms the safety profile of these agents and characterizes the essentially non-toxic nature of virtually all accidental pediatric exposures to LAAR's. Specifically, as it relates to proposed benefits of the proposed mitigation procedures, this publication confirms that virtually all pediatric exposures to these agents are "non-toxic", result in no injury, need no "treatment" nor medical intervention, and no hospital or emergency care is necessary. The guideline now represents the "standard of care" for poison centers and health professionals when responding to these incidents and will result in a precipitous drop in unnecessary referral for medical evaluation or treatment associated with theses exposures independent of implementing the proposed mitigation procedures.

As regards EPA's suggestion that there is an "emotional toll" on parents or care givers calling poison centers for assistance or information regarding LAAR exposures, there is simply no data to support this subjective contention. Poison centers routinely promote and advertise their free public service to aid consumers in determining if a given exposure, regardless of how trivial, might require some type of intervention. To suggest that there is an emotional toll associated with using the service is inappropriate,

unfounded and does not accurately reflect the experiences of those who make use of and provide such services.

Furthermore, EPA mandated labeling is another primary reason for calls to poison centers after unintended and inconsequential pediatric exposures to these agents. A more risk based labeling convention is needed and would address any question of "social toll" or "anxiety" on the part of parents or care givers that might be due to perceived LAAR toxicity based on currently mandated labeling.

Background:

EPA's Impact Assessment specifically discussed human toxicity issues in the sections entitled "Summary of Proposed Mitigations" and "Human Incidents." Both sections rely heavily on incident data derived from the annual report of the American Association of Poison Centers (AAPCC) which is also known as the TESS (Toxic Exposure Surveillance System). The TESS contains aggregated data from more than 60 poison centers nationwide. The dataset examined by EPA appears to be data retrieved directly from the publicly available TESS annual report rather than from a purchased subset of category specific data, which often allows a more detailed analysis.

Data retrieved from the publicly available annual report is useful but has significant limitations in regards to the level of detail provided on any given category of data. As an example, the table used to derive the majority of data for their analysis is an aggregated summary of severity outcomes for all exposures in a given class of product for all age groups and all reasons, lumped together. The significance of this fact is that outcomes by age and reason cannot be determined but rather are presented in aggregate form. Thus, for each severity outcome category reported (minor, moderate, major) it cannot be determined how many pediatric or adult patients are represented within each outcome category. Neither can one determine how many of the reported exposures seen in a health care facility were children, adults, or whether the incident was the result of an intentional or unintentional act.

The EPA analysis also contains subtle comments implying that data details that were not available from the AAPCC public reports suggest that numerous other patients not represented in the outcome severities may have unreported injury. This is exemplified by the statement "outcomes are known for less than half of the total exposures" which would imply that nothing is known about the more than 50% of outcomes not represented in their analysis.

It is important to understand how "outcomes" are categorized in the poison center documentation system. Each case is assessed as to its overall severity outcome. Outcomes depicted as "no effect"; "minor effect"; "moderate effect"; "major effect"; and "death"; are typically described as incidents with a "known" outcome because the poison center maintains contact with the reporter to a point where the outcome can reasonably be expected to reflect the patient outcome.

There are three additional outcome classifications that fall into the general category of "no follow-up." These include "no follow-up, nontoxic"; "no follow-up, minimal toxicity", and "no follow-up, potentially toxic". In the first category of "no follow-up, nontoxic" the incident is so trivial that use of poison center resources to call the reporter back is simply unnecessary. In the second category of "no follow-up, minimal toxicity", no adverse effects are reported to poison center staff at the time of the call and the specialist assesses that no more than minor effects are even possible. Use of poison center resources to follow-up with reporters in these incidents is also deemed unnecessary. For the 3 yr period included in the EPA analysis, these first two categories of "unknown outcome" incidents comprised more than 50% of all outcome categories in the poison center database. The final category of "no follow-up, potentially toxic" is typically used for incidents involving attempts at self-harm where an individual refuses to divulge contact information for follow-up by poison center personnel. Fewer than 5% of all incidents in the database fall into this category.

This clarification is important. In incidents involving pediatric exposures, family members or health professionals are quite cooperative with poison center personnel in sharing information and being open to follow-up if the case warrants. Given this fact, it would be expected that the vast majority of pediatric incidents involving rodenticides that were lumped into the "unknown outcome" category were actually outcomes indicating non-toxic or trivial exposures that would not produce any adverse effect of consequence.

Due to the date of publication of the Mitigation Decision by EPA and the subsequent publication of a landmark scientific article regarding a comprehensive review of pediatric exposures to long acting anticoagulation rodenticides (LAAR's), the EPA analysis did not include vital scientific information pertinent to this issue. This information unequivocally confirms the safety profile of these agents and characterizes the essentially non-toxic nature of the most commonly reported pediatric exposures. A detailed summary of that article is contained in a section found later in this document.

Specific comments regarding EPA human incident analysis:

EPA provided an analysis of poison center rodenticide incident data from a review of the 2002, 2003, 2004 annual reports of poison control center data published by the AAPCC. A number of assumptions that were presented are not accurate including:

- *(p 8) "The reported incident cases may only account for a quarter of the total cases that occur, especially those requiring inpatient or outpatient treatment"*

  EPA's rationale for the above statement appears to be based on two publications from 1983 and 1990 regarding reporting of poisoning incidents to poison centers. Both articles were published during the formative years of the national regional poison control movement. The availability of services, nature of exposures treated, referred or otherwise managed by poison centers have changed dramatically. Additionally, the "toxic exposures" referred to in the articles were typically comprised of adult intentional overdoses, a subset of poison exposures

where poison center involvement is not sought due to the familiarity by many clinicians with current poison treatment practices.

There is also no information to suggest that any unintentional pediatric exposures to rodenticides have "required" inpatient or outpatient "treatment". (see consensus panel review section). The term "treatment" is routinely used in the EPA document to connote care rendered to prevent or mitigate injury when in fact, the term as used in the referenced documents simply refers to the act of a patient presenting to a healthcare facility for evaluation. Additionally, the only specific treatment antidote available to "treat" actual poisoning from long acting anticoagulants is Vitamin K1 (Phytonadione). In the years 2002, 2003, 2004, out of 7,258,406 exposure incidents, there were only 1,766 instances where Vitamin K1 was administered for ***any*** reason including use in all cases of intentional ingestions of rodenticides or any case of bleeding from non-rodenticide pharmaceutical anticoagulants. That said, a more detailed analysis of a specific subset of poison center rodenticide exposures discussed later in this document did not identify one instance of an unintended pediatric exposure to a rodenticide resulting in clinical bleeding requiring any treatment.

- *(p 8)"The 3-year average (2002-2004) of the cases of unintentional illnesses are presented in Table 3."*

  Table 3 does not specifically identify one case of unintentional pediatric exposure that resulted in adverse effects or "illness". As explained in the introduction, the aggregated data in the AAPCC report is an aggregated summary of severity outcomes for all exposures in a given class of product for all age groups and all reasons lumped together and, pediatric unintentional exposures cannot specifically be identified in this dataset. As stated earlier a more detailed analysis of a specific subset of poison center rodenticide exposures which is discussed later in this document did not identify one instance of an unintended pediatric exposure to a rodenticide that resulted in clinical bleeding requiring any treatment.

- *(p 9)"Table 3 clearly shows that most reported cases (over 80 percent) occur in children less than 6 years of age. About 30 percent of the reported cases are treated in health care facility."*

  It is more accurate to note that about 30 percent of the reported cases were "presented" to a health care facility. There is no way to determine what percent of patients needed referral, needed treatment, or received treatment when reviewing data from this dataset.

- *(p 9)"For the known cases, no-effect outcomes account for more than 93 percent. These no-effect cases theoretically would not result in any medical cost, but the TESS data show that 23% of the no-effect cases incurred medical costs for health facility visits.*

EPA rightly points out that during their three year period of rodenticide exposure incident review, approximately 5,000 patients were seen in a health care facility. Although it is unknown how many were pediatric patients, given the preponderance of pediatric patients represented in this dataset, it would be reasonable to assume the majority of these were pediatric patients. One thing that has not been considered is the fact that the recently published "standard of care" approach for poison centers and other health care practitioners dealing with unintentional pediatric exposures to long acting anticoagulant rodenticides does not recommend any health care referrals for these patients. Thus, the reported numbers of patients currently being unnecessarily referred for evaluation in a health care facility can be expected to drop precipitously in the coming years.

- *(p 9) "In addition, there are likely to be costs associated with lost productivity for the time and anxiety associated with a call to a poison control center."*

  There is no data to support this assertion. Furthermore, it is ironic that EPA is suggesting that manufacturers' products should be sanctioned when consumers follow directions outlined in EPA-mandated labeling. EPA-mandated cautionary statements in current LAAR labeling communicates to consumers that *any* product contact is potentially dangerous. First aid labeling further directs consumers to "call a poison center immediately" for virtually any unintended contact with the product. Consequently, consumers do call for assistance and information when coming in contact with the product regardless of how inconsequential or non-toxic the exposure might be.

  For decades poison centers have been promoting their services and educating consumers to call for assistance with "any" unintended exposure even if there are no symptoms or if the caller believes the exposure is "non-toxic". For this specific reason, it is not surprising that 88% of all pediatric exposures reported to poison centers nationally result in no adverse effects or are deemed "non-toxic" in nature. It would make no sense to suggest that the products that are the subject of those calls should be sanctioned simply because consumers respond to poison center marketing efforts and use the service.

  Regarding the anxiety associated with a call to a poison center, it is unusual for any caller to be frantic with the typical LAAR related pediatric exposure. During the last 28 years, this author has personally responded to hundreds of poison center calls involving pediatric exposure to LAAR's. The callers typically report small ingestions of an inconsequential amount and are simply following EPA mandated labeling which advises that they should call for assistance to determine if they need to do anything. Additionally since none of the reported pediatric exposures has ever produced rodenticide related toxicity, there are no corresponding signs or symptoms of toxicity to produce anxiety on the part of the caller. Thus, calls to poison centers involving these exposures are unlikely to be any more stressful than calling to report any other non-toxic, unintentional

exposure such as many of the calls involving "cosmetics" which, as a class, has almost the same safety profile as rodenticides.

Response and Comment regarding other statements made by EPA in the Impact Assessment for Proposed Rodenticide Mitigation (DP 332577)

- *(p 3) (p 4) "Approximately 3% of reported exposures result in medical symptoms associated with rodenticide exposure (skin irritation, nausea, delayed blood clotting)*

  EPA has not presented any data supporting the premise that acute unintentional pediatric exposures to rodenticides have been "associated" with skin irritation, nausea, and delayed blood clotting. Additionally, skin irritation is not an expected adverse clinical effect resulting from dermal exposure to the long acting anticoagulant rodenticide products, and neither is nausea unless it could somehow be related to a bleeding diathesis, which also has not been reported in accidental pediatric exposures.

- *(p 9) "The health benefit associated with reduced illnesses and deaths can be measured"*

  First, there are no deaths in children from LAAR's or the other included rodenticides. Second, how can a "health benefit associated with reduced illnesses and death" be calculated when there is no specific illness reported for the types of exposures the Agency is trying to prevent? Additionally and as stated previously, the recently published consensus paper regarding the evidence-based consensus guideline for out-of-hospital management of LAAR's is expected to result in a precipitous decrease in hospital visits for unintentional exposures to LAAR's which comprise the largest percentage of reported health care visits for products in this class.

- *(p 24) "Most poisoning incidents involving exposure to second generation anticoagulants occur in children less than six years old,...."*

  The data presented by EPA does not support this statement. Inconsequential exposure in children is common, "poisoning" associated with single acute accidental exposure (the type of exposure involved in more than 99% of all pediatric rodenticide exposures) has not been reported.

- *(p 24) The proposed mitigation requiring that second generation anticoagulants be classified as "Restricted Use" should not have an adverse impact on homeowners,..."*

  The EPA has not truly considered how homeowners will react to loss of such effective rodenticide control measures, and whether they will rely upon less

effective and difficult to use applications (traps, bait stations, etc). These measures will create a void in available rodenticide control measures and consumers will likely find alternative approaches to achieve the success of previously available means. Alternative approaches may put children and pets at risk in yet to be determined ways.

New Published Data not included in the EPA proposed Risk Mitigation Procedures:

Subsequent to EPA releasing their proposed rodenticide mitigation proposal, a national medical consensus panel with input and consultation from 29 medical, scientific, regulatory and public health organizations published it's finding regarding risk of childhood poisoning from unintentional exposure to low concentration long acting anticoagulant rodenticides (LAAR's). This landmark white paper confirms previous safety assessment information provided to the EPA through the Rodenticide Taskforce. The report, published in the February 2007 Issue of the Journal *Clinical Toxicology*, is entitled "Long-acting anticoagulant rodenticide poisoning: An evidence-based consensus guideline for out-of-hospital management".

Key findings and considerations weighing in on the consensus panel conclusions include:

- In a review of more than 20,000 accidental exposures reported to poison centers over a 20 year period involving children under the age of 6 years, none have ever developed physical evidence of anticoagulant toxicity
- There has never been a recorded death in a child from any of the "blood-thinning" rat and mouse poisons
- There has never been a reported case of a child getting seriously ill as a result of "accidentally" ingesting any of these products.
- These products have such a wide margin of safety there is typically no need for any medical intervention after accidental exposure
- The panel further recommends that all poison centers and others responding to reports of accidental ingestions to these products, discontinue any medical referral to ER's, clinics, doctors offices or health care providers. This fact alone will likely have a significant impact on unnecessary hospital evaluation in pediatric exposures to these products. This is an outcome sought by the EPA in justification of their current risk mitigation proposal and *will* be accomplished independent of implementing the proposed use of child resistant bait stations.

Poison control experts and clinical toxicologists have provided additional information to the rodenticide manufacturers regarding their individual experiences in responding to reports of accidental ingestion to these products

including:

- The design of these products, which contain low levels of active ingredient in food based pellet or block bait, is simply not conducive to toxic ingestion by children
- The newly adopted "standard of care" guideline regarding management of these incidents is similar to that used in managing the most benign of pediatric exposures, such as exposures to personal care and non-toxic arts and crafts products which have a similar "evidence based" safety profile
- Current reports of exposures and subsequent unnecessary hospital visits have typically been driven by "over labeling" of these products in regards to potential risk of injury from unintended exposure.

Background Information Regarding the Genesis of the LAAR Consensus Panel Initiative

Composition of the Review Committee

The national review committee consisted of various members of the healthcare disciplines across the United States including physicians, pharmacists and nurses with expert clinical training in their respective field. These members comprised current and past directors of public poison centers in the United States as well as professors in colleges of pharmacy and medicine across the United States. In addition, the review committee was also represented by the following national organizations:

Ambulatory Pediatric Association
American Academy of Breastfeeding Medicine
American Academy of Emergency Medicine
American Academy of Pediatrics
American Association of for Health Education
American College of Clinical Pharmacy
American College of Emergency Physicians
American College of Occupational and Environmental Medicine
American Pharmacists Association
American Public Health Association
American Society of Health-system Pharmacists
Association of Maternal and Child Health Programs
Association of State and Territorial Health Officials
Canadian Association of Poison Control Centers
Centers for Disease Control and Prevention – National Center for Injury Prevention and Control
Consumer Federation of American
Consumer Product Safety Commission
Department of Transportation

Emergency Medical Services for Children
Emergency Nurses Association
Environmental Protection Agency
Food and Drug Administration
National Association of Children's Hospitals and Related Institutions
National Association of Emergency Medical Services Physicians
National Association of School Nurses
National Association of State Emergency Medical Services Directors
National Safe Kids Campaign
Teratology Society
World Health Organization International Programme on Chemical Safety

Data Reviewed

The Committee undertook a comprehensive review of the literature using all major biomedical databases, abstracts from national professional meetings, medical textbooks on poisonings and the entirety of the Toxic Exposure Surveillance System (TESS) - the central database for all public poison centers in the United States - to identify all relevant journal articles, abstracts and clinical trials involving these substances. Finally, the board elicited information and suggested guidelines from all public poison centers in the United States to develop their guidelines.

Conclusions Reached Regarding Children (age <6 years old or less)

- We have seen a steadily declining rate of total exposures among children of this age group over the past several years.

- Almost 98% of all cases of exposure among all ages result in symptoms no more severe than upset stomach and/or 1 or 2 episodes of vomiting. There has never been a reported case of a child dying or getting seriously ill as a result of "accidentally" ingesting any of these products.

- Although potential medical problems can arise among those intending to hurt themselves with these products, exposures that children of this age group typically have with such products do not require medical evaluation or treatment either in a local hospital's emergency department or physician's office.

- There is no need to cause a child to vomit, give them charcoal or administer any kind of antidote in cases where the parent has even found the child with several pellets in their mouth. Unless directed by a public poison center or physician to do so, almost all children can be left at home and observed by the parent(s) / guardian(s).

- Medical staff at public poison centers will often overestimate or take a "worst case scenario" when addressing an actual or potential exposure to any of these products, because of the nature of the concern voiced by the parent. They do not recommend the routine use of any antidote in these cases.

About the Author:

Dr. Rick Kingston is currently President, Regulatory and Scientific Affairs, SafetyCall International Poison Center (www.safetycall.com) and Clinical Professor of Pharmacy, University of Minnesota. Dr. Kingston has 28 years professional experience in the areas of clinical toxicology and pharmacology, poison control, and product post-market medical surveillance. Previously, Dr. Kingston served as vice president and co-founder of poison center services for PROSAR Inc. as well as co-founder and former Director of the Minnesota Regional Poison Center and its affiliated industry toxicology programs at St. Paul Ramsey Medical Center, in St. Paul, Minnesota. He has 23 years critical care toxicology experience gained from practice in a University affiliated Level One Trauma Center. He holds a joint academic appointment with the University of Minnesota at the rank of full Clinical Professor within the College of Pharmacy. Dr. Kingston completed his Bachelor of Sciences in Pharmacy degree at the University of New Mexico, his Doctorate in Clinical Pharmacy at the University of Minnesota, and a Post-Doctoral Fellowship in clinical toxicology and pharmacokinetics at St. Paul-Ramsey Medical Center and the University of Minnesota. In his academic capacity he serves in multiple areas related to his practice focus of "clinical toxicology and product safety".

Dr. Kingston was one of the original poison center directors to serve on the development team for the American Association of Poison Control Centers (AAPCC) Toxic Exposure Surveillance System (TESS) and has personally contributed ten's of thousands of incidents to the database during his poison center tenure. His current practice at the SafetyCall International Poison Center and it's affiliated "Pet Poison Helpline" has given him additional expertise in the management of human and animal exposure incidents involving long acting anticoagulant rodenticides and an intimate understanding of incident data associated with these products. SafetyCall provides adverse event management services for the leading rodenticide manufacturers in the United States. As such, SafetyCall's poison center responds to more rodenticide related consumer and health professional exposure inquires than any other poison center in the world.